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van der Stouwe, A M M; Everlo, C S J; Tijssen, M A J

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Review article

Which disease features run in essential tremor families? A systematic review

A.M.M. van der Stouwe*, C.S.J. Everlo, M.A.J. Tijssen

Department of Neurology, University Medical Center Groningen, Groningen, the Netherlands

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ABSTRACT

Essential tremor is a common and highly heritable movement disorder. It is largely unknown, however, to what extent family members share overlapping symptoms. Such knowledge would be useful, as it may lead to the definition of familial essential tremor phenotypes, which will aid the ongoing search for genotypes. Also, this information can be used by clinicians in patient counselling. Therefore, we conducted a systematic review to provide an overview of the evidence on which essential tremor features run in families, to assess the literature's strengths and weaknesses, and to provide recommendations for future studies. PubMed was searched resulting in 460 titles: sixteen articles ultimately proved fit for inclusion. The results are represented in line with the Axis 1 classification of tremor as published in the latest Consensus Statement. In summary, we found varying levels of positive evidence for familial aggregation of age at onset, disease progression, alcohol responsiveness, parkinsonism and dystonia. Evidence on midline tremor was conflicting. The evidence on familial clustering was negative for cerebellar signs and action tremor asymmetry. Although the level of evidence is modest, it seems that some disease features are indeed familial, while other features are not. We discuss complicating factors, such as state-vs-trait dependency of characteristics, the place of familial dystonia, and the development of diagnostic criteria for essential tremor over time. In the future, comprehensive replication studies are needed, with the addition of several characteristics that have not been investigated so far, as the next step towards discovery of essential tremor phenotypes.

1. Introduction

Essential tremor is a common cause of disability [1] and is considered to be a highly heritable disorder. Estimates for the proportion of essential tremor patients with a positive family history range from 20% to 90% [2–5]. It is largely unknown, however, to what extent family members share overlapping features.

Information on the familial aggregation of symptoms in essential tremor would be relevant scientifically, particularly in the field of genetics. In recent years, the search for disease related genes has intensified, by means of linkage analysis, whole exome sequencing and genome-wide association studies [6]. Despite these efforts, essential tremor genetics still await a breakthrough discovery that will improve the understanding of this disorder. A key issue is that the essential tremor syndrome transpires to be a family of diseases rather than a single disease entity [6–8]. The suggested way forward is to increase focus on phenotyping and phenotype-genotype association [6,8]: the International Parkinson and Movement Disorders Society's tremor task force especially chose a classification scheme that promotes detailed phenotyping in their 2018 Consensus Statement [8], to facilitate the discovery of specific (genetic) etiologies. Inspiration can be gleaned from recent discoveries in Tourette's syndrome, which is phenotypically complex because of its relationship with attention deficit disorder and obsessive-compulsive disorder, and where the identification of cross-disease phenotypes appears to add to gene-finding efforts [9,10]. In this regard, reviewing which disease features aggregate in families is a welcome contribution in essential tremor research, as it may provide focus for future efforts in genetic studies.

Likewise, knowledge about familial aggregation of essential tremor features would be relevant for patient counselling. Clinicians often care for patients who have several affected family members, as well as younger, at-risk relatives, most importantly children and grandchildren. For these patients, it would be informative to know whether the features in their family members can help predict their own disease course. Questions that may concern them may be:

> Does my age at tremor onset predict the age at onset of my child, who may be at risk of developing a tremor too?
>
> Are some families slower progressors and other families fasters progressors?
>
> Does the fact that my relative has an “embarrassing” head tremor

* Corresponding author. Department of Neurology, University Medical Center Groningen, PO Box 30.001, 9700 RB, Groningen, the Netherlands.
E-mail address: a.m.m.van.der.stouwe@umcg.nl (A.M.M. van der Stouwe).

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mean I will develop a head tremor too?

It would be valuable to enable clinicians to answer these questions.

To provide information on aggregation of familial features in essential tremor we conducted a review of the current literature. Our aims are to give an overview of the available evidence, to assess the literature's strengths and weaknesses, and to provide recommendations for future essential tremor family studies.

2. Methods

2.1. Search strategy

We conducted a systematic literature search according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) method. The population we were interested in consisted of patients with familial essential tremor. We defined the interest as heritability of clinical features. We searched the literature via PubMed using the search term (“family" [MeSH Terms] OR “family" [All Fields] OR “familial" [All Fields]) AND (“essential tremor" [MeSH Terms] OR (“essential" [All Fields] AND “tremor" [All Fields]) OR “essential tremor" [All Fields]). A targeted search of the references of the articles included was also performed to identify additional studies.

2.2. Inclusion criteria

One of the authors (AMS) reviewed the titles and abstracts of the 460 initial results based on the following criteria. The article had to be published in English before January 2018 and the abstract had to be available online. Papers were included for discussion if they met these two criteria: description of 1) symptoms and/or disease course, and 2) in families of essential tremor patients. Note that neither description of phenotypes of unrelated patients nor reports on genetic analysis of related patients without phenotypical information are relevant to our research question “Which disease features run in essential tremor families?“. As the lower limit for inclusion either more than one family or one large family (consisting of at least three generations with two affected patients per family) had to be described. Papers that were deemed eligible based on the abstract but were unavailable online were tracked by our center's Medical Library (n = 4).

2.3. Extracted information

We extracted the following data: the investigated characteristics, means of assessment, numbers of patients, numbers of families, whether there was evidence for familial aggregation and what statistical analysis had been employed.

2.4. Grouping of results

In the text, we will discuss the evidence per feature. In line with axis 1 of the 2017 Consensus Statement, we will first report on historical features, then on tremor characteristics, and finally on associated signs (see Fig. 1 in Consensus Statement). As we found no studies reporting on the heritability of laboratory tests (electrophysiology, imaging), we have nothing to report in this category.

3. Results

3.1. Search results

Our search resulted in 460 titles, 351 of which were rejected based on titles and abstracts alone. One-hundred-and-nine full length articles were assessed, fifteen of which were included. A final article was added from the references of the first fifteen. Reasons for exclusion were 1) the topic is another movement or tremor disorder (orthostatic tremor, familial cortical myoclonic tremor with epilepsy, etc. (n = 145)), 2) the study did not report on clinical symptoms *per* family (n = 103), 3) the paper is a review article (n = 71), 4) the paper focusses on genetics without providing information about clinical symptoms *per* family (n = 48), 5) a single small family is investigated (n = 31), 6) the topic is treatment (deep brain stimulation, medication (n = 14)), 7) the paper reports an imaging study (n = 13), 8) the study only investigated unaffected relatives or healthy individuals (n = 7), 9) the paper reports a pathology study (n = 7), 10) the study is in non-human subjects (n = 6). In the papers on treatment, imaging and pathology, these topics were not investigated in related patients, thus they are unhelpful in answering the research question. Fig. 1 presents a flow-chart of the inclusion process.

4. Historical features

An overview of historical features can be found in Table 1, including the diagnostic criteria [11,12] used for inclusion.

4.1. Age at onset

Whether age at onset aggregates in families was investigated in 26 probands and 52 family members in a genetics study at Columbia University [13]. Probands had to have an age at onset ≤ 40, later revised to ≤ 50 to be more inclusive. All participants underwent an in-person evaluation, including a videotaped examination, which was reviewed by an experienced neurologist to confirm all diagnoses. Age at onset was defined as the self-reported age at which patients first noticed their tremor. To minimize ‘age-at-interview bias’ data from offspring who were younger than their parents were at the age of disease onset were excluded. The correlation between probands' and relatives' age at onset was significant yet moderate in effect (reported Pearson's $r = 0.50$, $p = 0.001$). Similar results were found in a pedigree-averaged analysis and held up in proportional hazards regression models. In approximately 60% of cases, relatives' age at onset was within a 10-year distance of the probands' age at onset, meaning that 40% of the time, the difference in age at onset exceeded 10 years. No evidence was found for genetic anticipation, as only 9/18 children reported an earlier age at onset than their participating parents. There are earlier reports on large single families suggesting anticipation of age at onset [14,15], but these findings may well be attributed to ascertainment bias [16] or age-at-interview bias [17] and are therefore not included in this overview.

4.2. Rate of progression

There is one paper published on between-family heterogeneity in rate of progression, by the group at Columbia University [18]. Seventy-eight essential tremor patients were investigated in this study, from 23 families. As participants only paid one visit, disease progression had to be extrapolated: the rate of progression was defined as the total tremor score/log (disease duration in years). An analysis of variance gave evidence of heterogeneity in the log rate of progression across families ($p < 0.001$) with more than half (55.4%) of the variance explained by the family grouping. Adjusting for age at onset, as older age at onset was associated with a faster rate of progression, did not change the results. A four-fold difference in rate of progression was observed between families.

4.3. Alcohol responsiveness

In a study on hereditary essential tremor, Bain et al. investigated 91 patients from 20 families [19]. Half of the patients reported alcohol responsiveness. In 80% of families, responsiveness was either consistently present or absent (ratio responsive versus unresponsive families = 4:1), while 20% of the self-reported effect of alcohol was heterogenic. This hints at familial aggregation, but only descriptive

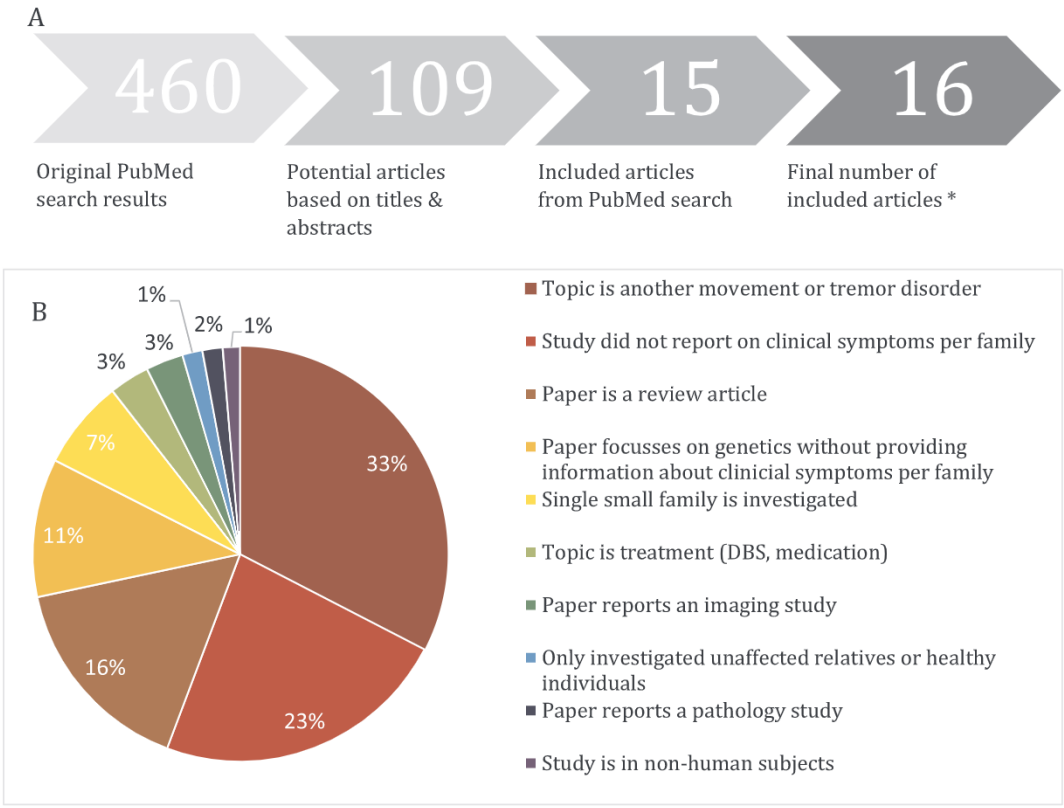

Fig. 1. A) Flowchart of included and excluded articles. * One article was added from the references of the first fifteen. B) Specification of reasons for exclusion (n = 445).

statistics were employed. A recent study investigated alcohol responsiveness in a large cohort of essential tremor patients using a validated and published home test [20]. Here, it was found that a positive family history of essential tremor did not correlate with alcohol responsiveness, however: whether (un)responsiveness aggregates in particular families was not investigated and thus remains unknown. Additionally, in another study, the same group showed that both a positive family history and reported alcohol responsiveness is more common in early-onset than in late-onset patients (75% versus 59%, and 76% versus 45%, respectively) [21]. This suggests an interplay between the three features age at onset, alcohol responsiveness and a positive family history, although these correlations were not explicitly examined in this study. Again, whether these features co-aggregate in essential tremor families was not investigated so the relationship can only be speculated about.

5. Tremor characteristics

In Table 2, an overview is presented of our findings on tremor characteristics.

5.1. Midline tremor

A large, Scandinavian population based-study published in 1960 described 211 essential tremor cases from a small number of ancestral families in which cervical tremor was present in some members of some but not all families, hinting at familial aggregation [22]. However, only 81 cases were examined in person, and the investigators did not pay attention to confounding factors. Moreover, diagnostic accuracy is doubtful as the reported additional neurological signs include rigidity and stiffness, and no explicit information on dystonia is given, although this is particularly relevant as cervical tremor may be dystonic.

More recently, the group at Columbia University investigated the familial aggregation of midline tremor in essential tremor [23]. Ninety-five patients participated in this study, from 27 families, after exclusion of patients with dystonia. Midline tremor was included in a videotaped neurological assessment. Voice tremor was assessed during sustained phonation, spontaneous speech and reading, cervical tremor was examined at rest, and jaw tremor was assessed with mouth closed, open, during sustained phonation and spontaneous speech. Midline tremor was then considered as either present of absent, based on the pooled assessment of the aforementioned features. Additionally, a separate analysis was done for cervical tremor. 23 of the 28 families (82%) included both relatives with and without midline features, indicating a high degree of within-family heterogeneity. Pearson's correlation, bivariate and multivariate logistic regression models demonstrated that presence of midline tremor in one patient did not predict midline tremor in other relatives (all $p > 0.05$). Age, disease duration and severity were found to be predictive, but not familial factors.

5.2. Action tremor asymmetry

The familial occurrence of asymmetry in action tremor was investigated in 187 patients from 59 families in a genetic study by a group at Yale and Columbia University [24]. Tremor examinations were videotaped, and one experienced neurologist scored all videos. Patients performed 12 different tasks per arm [25]. The tremor asymmetry index was determined by right arm minus left arm tremor score. A bivariate linear regression model showed that the tremor asymmetry index in one patient was not a predictor of the tremor asymmetry index in their relatives ($p = 0.66$). Likewise, in an ANOVA, family grouping did not explain a significant proportion of the total variance in tremor asymmetry index ($p = 0.56$).

Table 1
Overview of publications on familial aggregation of features in essential tremor: historical features.

Publication	Diagnostic criteria used for inclusion	Symptom(s)	Assessment	No. of patients	No. of families	Evidence of familial aggregation Y/N	Statistics
Louis, 2013, *Neuroepidemiology*	'Possible ET' as defined by the WHIGET criteria in absence of PD or other known cause	Age at onset	Self-reported age at onset	78	26	Yes: significant correlation, moderate effect	Pearson's R = 0.5, $p = 0.001$. Proportional hazards linear regression: similar
Louis, 2013, *Parkinsonism & related disorders*	'Possible ET' as defined by the WHIGET criteria in absence of PD or other known cause	Rate of progression	Total tremor score/log (disease duration)	78	23	Yes: 4-fold difference in rate of progression across families	ANOVA, $F = 3.11$, $p < 0.001$, 55% of variance explained by family grouping
Bain, 1994, *Brain*	'Definite ET' as defined by the TRIG criteria for probands, 'possible ET' for relatives	Alcohol responsive-ness	In person neurological assessment Self-reported alcohol responsiveness	91	20	Hint: alcohol responsiveness consistently present or absent in 80% of families, mixed in 20% of families.	Descriptive statistics

ET: essential tremor, WHIGET: Washington Heights-Inwood Genetic Study of Essential tremor [11], TRIG: Tremor Investigation Group [12].

Table 2
Overview of publications on familial aggregation of essential tremor features: tremor characteristics.

Publication	Diagnostic criteria used for inclusion	Symptom(s)	Assessment	No. of patients	No. of families	Evidence of familial aggregation Y/N	Statistics
Louis, 2013, *Neuroepidemiology*	'Possible ET' as defined by the WHIGET criteria in absence of PD or other known cause	Cranial tremor	Videotaped assessment: Voice tremor in sustained phonation, spontaneous speech, and reading. Cervical tremor at rest. Jaw tremor with mouth closed, open and during speech.	95	27	No	Pearson's correlation coefficient, bivariate and multivariate logistic regression models, all $p > 0.05$
Larsson, 1960, *Acta Psychiatrica Scandinavica*	No specified criteria. In line with 1960s' consensus patients are 'mainly mono-symptomatic'	Cranial tremor	81 patients via in person neurological assessment, 130 patients via heteroanamnesis	211	6	Hint: cranial tremor was present in some members of some families	Descriptive statistics
Louis, 2017, *Frontiers Neurology*	'Possible ET' as defined by the WHIGET criteria in absence of PD or other known cause	Action tremor asymmetry	Videotaped assessment: difference between right and left arm tremor score	187	59	No	Pearson's correlation coefficient, bivariate logistic regression models, ANOVA, all $p > 0.05$

ET: essential tremor, WHIGET: Washington Heights-Inwood Genetic Study of Essential tremor [11].

Table 3
Overview of publications on familial aggregation of essential tremor features: associated signs.

Publication	Diagnostic criteria used for inclusion	Symptom(s)	Assessment	No. of patients	No. of families	Evidence of familial aggregation Y/N	Statistics
Louis, 2017, *Tremor and Other Hyperkinetic Movements*	'Possible ET' as defined by the WHIGET criteria in absence of PD or other known cause	Cerebellar signs	Videotaped assessment: Intention tremor via finger-to-nose maneuvers & Tandem gait difficulty	187	59	No	Bivariate and multivariate logistic regression models, all $p > 0.05$
Hedera, 2010, *BMC Neurology*	Bilateral postural & kinetic tremor without any other neurological signs (excl dystonia, see main text). Score employed: WHIGET.	Dystonia	In person neurological assessment	463	97	Yes: all patients with dystonia were distributed over 28% of families	Chi-square test, $p < 0.001$
Louis, 2012, *Parkinsonism & Related Disorders*	'Possible ET' as defined by the WHIGET criteria in absence of PD or other known cause	Dystonia	Videotaped neurological assessment	100	28	Hint: all patients with dystonia were distributed over 28% of families	Descriptive statistics
Shatunov, 2006, *Brain**	Bilateral tremor, duration > 5 years, moderate-severe tremor	Dystonia	In person neurological assessment	44	5	Hint: all patients with dystonia were distributed over 40% of families (i.e. 2 families)	Descriptive statistics
Ma, 2006, *Tremor and Other Hyperkinetic Movements*	'Definite ET' as defined by the TRIG criteria, or 'probable ET' in case of offspring with 'definite ET'	Dystonia	In person neurological assessment	64	4	Hint: all patients with dystonia were female and belonged to 25% families (i.e. 1 family)	Descriptive statistics
Jankovic, 1997, *Archives Neurology*	'Possible ET' as defined by the TRIG criteria	Dystonia	In person neurological assessment	84	4	Hint: all patients with dystonia were distributed over 75% of families (i.e. 3 families)	Descriptive statistics
Bain, 1994, *Brain*	'Definite ET' as defined by the TRIG criteria for probands, 'possible ET' for relatives	Dystonia	In person neurological assessment	91	20	Hint: no dystonia was encountered	Descriptive statistics
Cohen, 1987, *Movement Disorders*		Dystonia	In person neurological assessment	7	1	Hint: 2 patients ET, 2 patients writer's cramp, 1 both, 1 writing tremor	Single family
Yahr, 2003, *Parkinsonism Related Disorders*	Unclear	Parkinsonism	In person neurological assessment	11	1	Hint: 11 ET of whom 3 PD (including twin brothers)	Single family
Pushman, 2011, *Neurology*	Postural upper limb tremor, gradual onset, > 1 year	Parkinsonism, RLS	In person neurological assessment, self-reported RLS	30	1	Hint: 19, ET, 5 PD, 6 both; 15 RLS, 7 of which also had ET and/or PD.	Single family
Gulsunar, 2014, *PNAS*	'Possible ET' as defined by the TRIG criteria	Parkinsonism	In person neurological assessment	16	1	Yes: 11 ET, 5 ET + PD, with missense HTRA2 p.G399S mutation	Single family + whole exome sequencing
Leng, 2017, *J Human Genetics*	'Possible ET' as defined by the WHIGET criteria in absence of PD or other known cause	Familial episodic pain	Questionnaires + video-taped neurological assessment + polymyography	10	1	Yes: 10 episodic pain, 8 ET, with gain-of-function p.Arg225Cys in SCN11A	Single family + whole exome and Sanger sequencing
Neuhauser, 1976, *Clinical Genetics*	Unclear	(Congenital) nystagmus + duodenal ulcers	In person neurological assessment?	17	1	Hint: all 17 patients were affected by a combination of ET, nystagmus and ulcers	Single family

ET: essential tremor, WHIGET: Washington Heights-Inwood Genetic Study of Essential tremor [11], TRIG: Tremor Investigation Group [12], PD: Parkinson's disease, RLS: restless legs syndrome. *The study by Shatunov et al. reports on 7 families: because 2 of the families are already described in the study by Jankovic et al., in 1997, we have excluded those patients from the study by Shatunov et al. in this table.

6. Associated signs

In Table 3, our findings on associated signs are summarized.

6.1. Cerebellar signs

While the hallmark of essential tremor is a bilateral upper limb action tremor, several cerebellar features have been described. Recently, these features were discussed in the new Consensus Statement [8], and categorized under the diagnosis 'essential tremor plus'. Cerebellar signs were assessed in 187 patients from 59 families, at Columbia University [26]. Specifically, the hypothesis was tested that the presence of intention tremor and tandem gait difficulty runs in families. Intention tremor was scored as either present (definite intention tremor in one limb, or probable intention tremor in two limbs) or absent, based on ten videotaped finger-to-nose maneuvers. Tandem gait was scored as present if the number of missteps out of ten steps exceeded two (representing the upper quartile of tandem missteps), again based on video recordings and rated by a neurologist with ample expertise. Bivariate and multivariate logistics regression models were used to predict cerebellar symptoms in relatives: however, the presence of cerebellar signs in probands did not predict cerebellar signs in the relatives in any model (all $p > 0.05$). Major predictors in this study were disease duration and severity, but not familial factors.

6.2. Dystonia

There has been much debate on the subject of dystonia and dystonic tremor versus essential tremor, and recently [8] the presence of dystonia was ruled as an exclusion criterion for the diagnosis essential tremor. However, some essential tremor patients do have relatives with dystonia. This was demonstrated already in 1987, when a three-generation family was reported that contained two relatives with essential tremor, two with writers' cramp, one with both, and one with writers' tremor [27]. This was before consensus criteria for essential tremor existed. Since then, several studies have examined the familial aggregation of dystonia in essential tremor, the largest and most thorough of which was conducted at the Vanderbilt University, where 463 patients from 97 families participated [28]. Probands were included with essential tremor with (n = 9) or without (n = 88) dystonia. All participants were examined in person, and cases of presumed secondary dystonia were excluded. Twenty-one percent of patients had dystonic signs, 89% of which had dystonia *not* affecting the upper limbs, mostly focally (cervical, laryngeal, blepharospasm, limb) and less often segmentally (craniocervical). The other 11% of patients with dystonic signs were relatives with cervical dystonia or blepharospasm without any tremor. Clustering of the patients with dystonia amongst 28% of families was analyzed using a Chi square test, demonstrating that dystonic symptoms were not distributed randomly but aggregated in specific families ($p < 0.001$).

Multiple other papers report on families with essential tremor and dystonia, which only employ descriptive statistics, but nevertheless hint at familial aggregation. In an earlier study aimed at inheritance patterns, published in 2006, the same group at Vanderbilt University reported on four families in which "several women" in one family were found to have cervical dystonia in addition to essential tremor [29]. In that study, families were included if at least 10 affected individuals were able to participate and subjects were only included if they met the then current criteria for definite essential tremor or probable essential tremor if they had relatives with definite essential tremor. All patients were examined by one of two movement disorders specialists, paying attention to additional movement disorders. Sixty-five patients were included from four families: in one family, several women had mild cervical dystonia, but their upper limb tremor was without any dystonic component. The affected men in this family all had typical essential tremor without dystonia, and several male offspring of women with cervical dystonia exhibited only the essential tremor phenotype. In a study similar to the one described under *Age at onset*, where 100 patients participated, Louis et al. also found 9 out of 28 (28%) families to have dystonic features [30]. In 1997, Jankovic et al. described four essential tremor families [31]. Out of 251 relatives, 84 had possible, probable or definite essential tremor as defined by the TRIG criteria [12]. In three of the four families, 11, 12 and 18 family members had dystonia, in the presence of tremor in 65% of these patients. Only one family had "pure" essential tremor. In a follow-up paper published in 2006[32], the same group reports a genetic study in which five more families are investigated. Out of the newly investigated 44 patients, 15 had dystonia in the form of writer's cramp (n = 11) or cervical dystonia and writer's cramp (n = 4): these patients all belonged to 2 families, while no dystonia was reported in the other 3 families.

6.3. Parkinsonism

Whether there is a relation between essential tremor and Parkinson's disease has been under investigation for a long time [33,34], but whether the two disorders aggregate in families has not been systematically investigated. There are several descriptions of single families, the oldest of which was published in the Indian Medical Gazette in 1943 [35]. It contains a diagram that "demonstrates at a glance the essential points of interest about this family": a two-generation family with six individuals with either "familial tremor", Parkinson's disease, or both. While this early paper does not meet our current standards for inclusion, three other publications do. In 2003, a five-generation family was described in which 11 relatives had essential tremor [36]. Among these where three brothers, two of whom were identical twins, with essential tremor before the age of 20 and Parkinson's disease after the age of 50, which was later confirmed on autopsy. Similarly, in 2011, a large family was reported containing 38 relatives with essential tremor, Parkinson's disease and/or restless legs [37]. Finally, in 2014, a Turkish, six generation consanguineous family was described in which 16 patients were investigated [38]. Eleven of these relatives had essential tremor, whereas five had a combination where essential tremor had preceded the onset of Parkinson's disease. After whole exome sequencing, HTRA2 p.G399S was identified as the likely responsible allele. Homozygosity was associated with earlier age at onset and severity of essential tremor than in heterozygotes, and only homozygotes developed parkinsonism in middle age. HTRA2 p.G399S leads to mitochondrial dysfunction, and this study suggests that in some families it is responsible for essential tremor and Parkinson's disease. However, the role of this variant remains doubtful, as no support was provided in follow-up studies [39,40].

6.4. Other sporadically reported associated signs

Finally, we would like to mention two reports of associated signs in essential tremor in single large families. First, there is a recent publication on a four generation Chinese family in which 10 relatives had familial episodic pain, a rare autosomal dominant disorder characterized by recurrent attacks of pain [41]. The onset of the episodic pain was during childhood, while onset of essential tremor was during adulthood: the two children investigated did not have a tremor yet, the eight adults did. After whole exome and Sanger sequencing, a missense mutation in the SCN11A gene was identified as causative in this rare hereditary syndrome.

Second, in 1976, a five-generation Swedish-Finnish family was described in which 17 relatives were affected by an alcohol responsive tremor, (congenital) nystagmus and/or duodenal ulcers [42]. This particular syndrome has never been described since.

7. Discussion

In this paper, we aimed to review the available evidence on familial

aggregation of features in essential tremor. To summarize, we found evidence for familial aggregation of age at onset, disease progression, alcohol responsiveness, parkinsonism and dystonia. Evidence on midline tremor was conflicting. The available evidence on familial clustering was negative for cerebellar signs and action tremor asymmetry. Although there are limitations to the evidence, it appears that some features are familial, while others are not. Yet, if we aspire to understand more about the clinical syndrome and pathophysiology of essential tremor, it is imperative that additional studies are done, as we will discuss below.

In terms of weaknesses and strengths, it emerges that many features are only covered by one paper, and thus lack replication. Moreover, one particular group has done a lot of the work, resulting in a potential for biases: it is conceivable that regional differences exist in essential tremor phenotypes, which remain unrecognized if the studies are not repeated elsewhere. Another point is that some, usually older papers use only descriptive statistics: their findings are suggestive of familial aggregation but lack explicit proof. A strength is that most studies report on decently sized groups, the largest including 463 participants. Also, most clinical features are assessed in real life by experienced neurologists and/or videotaped, resulting in proper appreciation of symptoms.

A problem in any review on essential tremor is that its' criteria for diagnosis have evolved over time. Patients that were previously included as essential tremor patients, in older studies, might not be included today. A typical example is the presence of dystonia: its' compatibility with a diagnosis of essential tremor was up for debate for a long time and was recently ruled as an exclusion criterion. We did decide to discuss this symptom in our review, because some patients that are rightfully diagnosed as essential tremor do have relatives with dystonia. To ignore this reality would be misrepresenting the complexity of the phenotype/genotype factors at play. In line with the recent consensus statement, we feel that careful documentation of clinical symptoms, without immediate judgment or jumping to conclusions, is the best way forward [8]. Such care is well-illustrated, for example, by Hedera and colleagues [28]. Moreover, patients should henceforth be labelled as ‘essential tremor plus’ if additional features are found [8], which after reclassification of a cohort of essential tremor patients led to relabeling in the vast majority of cases [43].

A second inherent problem in investigating familial aggregation of features is the consideration whether these features are related to ‘traits’ or to ‘states’. To use cervical tremor as an example: is the accumulation of a cervical tremor related to a certain essential tremor subtype (trait), or is it simply related to disease progression (state)? It is well established that the prevalence of cervical tremor increases with disease duration and disease severity [23,44], indicating a disease ‘state’ dependency. Nevertheless, there is evidence for a ‘trait’ relation as well: 1/3 of patients do not accumulate cervical tremor after a disease course of more than 40 years [44], while others develop cervical tremor early on, and it is even described in self-reportedly “unaffected” essential tremor family members [45]. Another study found that patients with cervical tremor differed from patients without on several demographic and clinical variables, suggesting that these patients present a distinct phenotype [46]. These findings were replicated, while simultaneously the prevalence of cervical tremor increased with disease duration in the same cohort [47]. To conclude: both state and trait factors are in play in the development of cervical tremor, and the same may be true for other symptoms (cerebellar symptoms). This is relevant for family studies, as relatives with shorter disease duration may still accumulate such a symptom: disease duration needs to be taken into account. Moreover, it seems that even the features that run in essential tremor families do not appear in all family members, reflecting the phenotypic heterogeneity that is associated with essential tremor.

Several recommendations can be made for future research endeavors. Firstly, larger and more comprehensive cohorts need to be studied, possibly internationally. Replication studies are highly desirable. Moreover, because so many features are involved, analyses that take into account multiple factors, such as principle component analysis or machine learning, should be considered. Genetic studies deserve special attention here: several large genetic studies have been performed in essential tremor, some of which with rigorous clinical evaluation of patients and stringent application of diagnostic criteria [48,49]. However, these studies commonly employ phenotype information exclusively as a means for diagnosis, not to investigate the heritability of disease features. The paper by Shatunov and colleagues [32] is an exception and could therefore be included (see Table 1). Others have attempted genotype-phenotype association between the dopamine D3 receptor 312A→G variant and age at onset and disease severity [50,51], which was not successful in the end [52–56]: this variant is currently believed not to play a role in essential tremor pathophysiology [57], and therefore these studies are not included in our analysis.

Secondly, several features of interest have not been studied yet: whether responsiveness to medication accumulates in families would be very interesting to know from a treatment perspective. If it is indeed true that alcohol responsiveness runs in families, as is hinted at by Bain and colleagues [19], the same may be true for beta-blockers or antiepileptic medication. Other symptoms that spring to mind are clinical neurophysiological features and non-motor features including cognitive and psychiatric symptoms. Some work has been done in this area: for instance, Fabbrini and colleagues found that depression is more prevalent in essential tremor patients with a positive essential tremor family history [58], however, whether depression clusters in certain essential tremor families remains unknown.

To summarize, if we wish to inform our patients correctly in the future, and if we wish to make progress in the understanding of essential tremor pathophysiology, studies that have a comprehensive approach to both phenotyping and next generation genotyping will be crucial.

In this review, we presented an overview of the available evidence on familial aggregation of features in essential tremor families. This information is of relevance both in the setting of genetic research and in the setting of the outpatient clinic. In the future, comprehensive studies are needed including symptoms that remain uninvestigated so far.

Declaration of competing interest

Nothing to report.

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